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DEVELOPMENT OF AN ON-DEMAND, GENERIC, DRUG-DELIVERY SYSTEM

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The objective of this research program was to develop an on-demand, generic, drug-delivery device. Specifically, this device would provide antidote for extended periods to persons exposed to chemical-warfare agents. The work involved development of a driving mechanism for drug injection, as well as fabrication of the delivery hardware. Three different driving mechanisms for controlled drug injection (osmotic, enzymatic, and acid/base) and a working prototype were developed. For ease of evaluation a water-soluble dye was used in place of drug during tests of the prototype. The device was successful in that it delivered a bolus of dye and then sustained a measured delivery of a different dye over an extended period. The device is also capable of delivering a large variety of soluble agents in a controlled manner, and parameters of the specific driving mechanism may be varied to alter the amount or rate at which the agent is delivered.

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SUMMARY

The Office of Naval Research has an interest in developing an on-demand, generic, drug-delivery system for administering antidote formulations to Navy personnel exposed to chemical-warfare agents. A device providing the controlled delivery of antidote is desirable because in many cases the antidote itself produces debilitating side effects if administered in too large a dose or if administered unnecessarily. Considering the relatively large number of different agents available for use against the military, it is also desirable that the drug-delivery system be able to administer a number of different antidotes equally well. It is desirable that the device function effectively for up to seven days. Southern Research Institute has conducted a nine-month program directed toward the development of an on-demand, generic, drug-delivery system that satisfies the criteria stated above.

This is our Final Technical Report on Contract N00014-84-C-0361, entitled "Development of an On-Demand, Generic, Drug-Delivery Device." This report covers work performed from June 1, 1984, to July 31, 1985. During this period, we have investigated three prototype mechanisms (osmotic, enzymatic, and acid/base) for providing a driving force for the controlled delivery of water-soluble pretreatment drugs or antidotes. We have also designed and fabricated a demonstration prototype of the delivery hardware, and the utility of the hardware and each driving-force mechanism has been assessed.

The demonstration prototype was purposely constructed on a larger scale than the anticipated field unit so that it would be easy to handle and any recommended design changes could be easily incorporated and evaluated. We decided to use a tooled prototype rather than an injection-molded one so that these changes could be made without incurring the expense that would be entailed by mold retooling. The device is all-aluminum construction, excluding gaskets and sealing materials. Aluminum was selected as the construction material because of the ease of tooling.

The demonstration prototype consists of a central plunger and drug reservoir, enclosed by a larger drug reservoir on each side. The central plunger, which delivers the initial bolus of drug, is spring actuated. The reservoir on each side is activated by rotating the central plunger and releasing a rupture pin. Drug from the side reservoirs is delivered to the needle by capillaries which communicate through the central plunger via O-ring sealed ports.

Despite preliminary problems with seating and sealing of the device, the systems developed thus far in the program demonstrate promise for use in producing a smaller, field-sized unit for use by military personnel.

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I. INTRODUCTION

In this contract we have investigated three prototype mechanisms (osmotic, enzymatic, and acid/base) for providing a driving force for the controlled delivery of water-soluble pretreatment drugs or antidotes. We have also designed and fabricated a demonstration prototype of the delivery hardware, and the utility of the hardware and each driving force mechanism has been assessed. The following sections describe the experimental details of our research efforts. These include osmotic, enzymatic, and acid/base systems for displacing drug from the storage reservoirs; fabrication of a demonstration prototype of the generic drug system; and an in vitro evaluation of prototype performance.

II. MATERIALS AND METHODS

A. Evaluation of Drug Displacement Systems

1. Osmotically powered systems

Five semipermeable materials (cellulose acetate, cellulose acetate butyrate, ethyl cellulose, ethyl hydroxyethyl cellulose (EHEC), and polysulfone) were evaluated for their film-forming ability and their permeability to water. Information pertaining to these materials as well as other compounds used to evaluate the osmotically powered systems is shown in Table 1.

a. Preparation of membranes

Each cellulosic material was dissolved in methyl ethyl ketone (MEK) to yield a 16.7% solution by weight. The Udel polysulfone was dissolved in chloroform to give a 15% solution by weight. Membranes were cast on a glass plate using an 8-in. doctor blade with micrometer adjustments (available from Pacific Scientific). A thin film of Liqui-Nox surfactant was used on each plate as a release agent for the membranes. Cellulosic membranes were cast using at least two of the following micrometer settings: 5, 10, and 15 mils. The polysulfone membrane was cast using a 15-mil setting. Each film was dried overnight under vacuum to remove residual solvent.

b. Measurement of water flux through membranes

Water-flux measurements were performed using the apparatus shown in Figure 1. In each measurement a 4.9-cm^2 membrane sample was placed over the opening as shown. The salt-solution compartment contains approximately 6 mL when filled to the zero mark. Salt solution was introduced into the chamber through the addition port and then sealed with a septum. The membrane side of

TABLE 1. MATERIALS USED OR EVALUATED IN STUDY

Material	Lot No.	Manufacturer	Location
DL-Aspartic Acid	12F-0399	Sigma Chemical Co.	St. Louis, MO
Boric Acid	BX870	MCB Manufacturing Chemists	Cincinnati, OH
Calcium Carbonate	5113 DK	Aldrich Chemical Company, Inc.	Milwaukee, WI
Cellulose Acetate	AC 31821	Eastman Chemicals	Kingsport, TN
Cellulose Acetate Butyrate	C-4404	Eastman Chemicals	Kingsport, TN
Ethyl Cellulose	112271	Dow Chemical Co.	Midland, MI
Ethyl Hydroxyethyl Cellulose	5193	Hercules Inc.	Wilmington, DE
Formic Acid, 88%	705470	Fischer Scientific Co.	Fair Lawn, NJ
Liqui-Nox	--	Alconox Inc.	New York, NY
Methyl Ethyl Ketone	KLKJ	Sargeant Welch Co.	Skokie, IL
Phosphoric Acid, 85%	2796 KVKE	Mallinckrodt	Paris, KY
Sebacic Acid	P612	Eastman Organic Chemicals	Rochester, NY
Silicone Oil, 350 cps	--	Dow Corning Corp.	Midland, MI
Sodium Bicarbonate	138376	J.T. Baker Chemical Co.	Phillipsburg, NJ
Sodium Chloride	702151	Fischer Scientific Co.	Fair Lawn, NJ
Stearic Acid	781427	Fischer Scientific Co.	Fair Lawn, NJ
Succinic Acid	237	Eastman Organic Chemicals	Rochester, NY
Tannic Acid	KHTZ	Mallinckrodt	Paris, KY
D-Tartaric Acid	AC 012087	Aldrich Chemical Company, Inc.	Milwaukee, WI
Udel Polysulfone	83-019	Union Carbide	Danbury, CT
Urea	68C-0123	Sigma Chemical Co.	St. Louis, MO
Urease Tablets	112F60713	Sigma Chemical Co.	St. Louis, MO

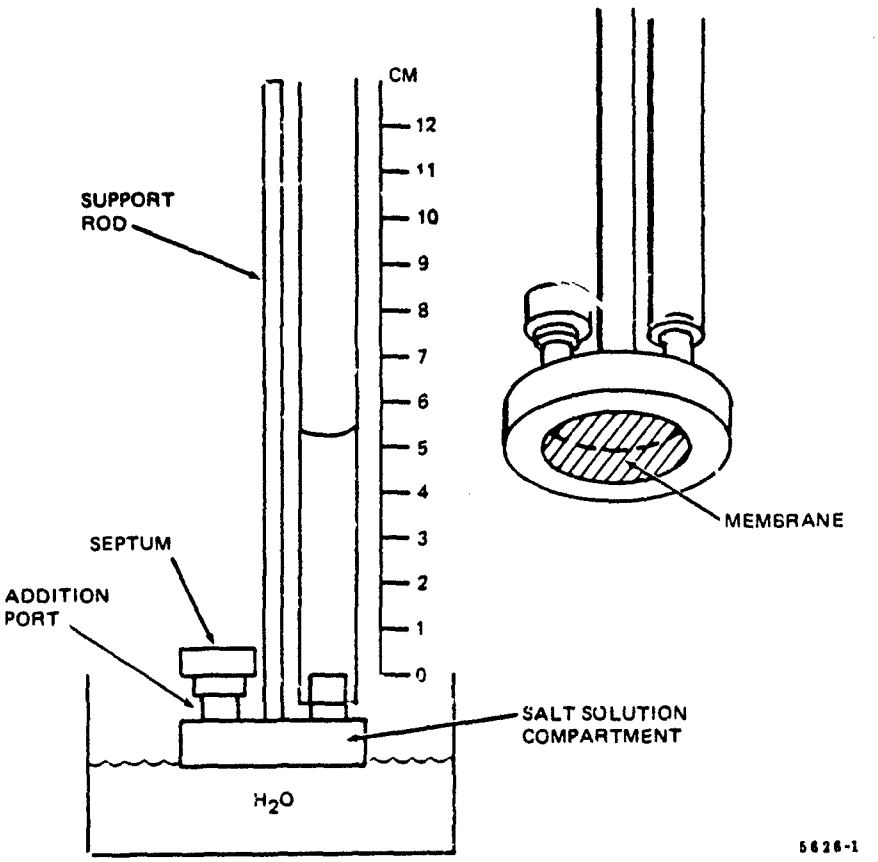

Figure 1. Apparatus for measurement of water flux through membrane.

the device was then placed in contact with a reservoir of the Milli-Q water contained in a thermostated bath. Water transport across the membrane was determined by measuring the resultant rise in capillary height of the attached column, which was left open to the atmosphere. The volume of fluid transported with time was then calculated from the column cross-sectional area and height change.

2. Gas-generating systems

Two systems were evaluated for CO_2 evolution. The first of these was an enzymatic system based on urea and urease. The second system was based on the formation of CO_2 by the reaction of acids with inorganic carbonates. Information regarding materials used in the gas-generating systems is found in Table 1, as noted previously.

a. Preparation of buffered enzyme/substrate solutions

All solutions were prepared by dissolving 1.5 g of urea in 10 mL of the buffer to be evaluated. The pH of the solution was then adjusted by the addition of concentrated sodium hydroxide solution. A Radiometer PHM 84 Research pH Meter was used to monitor pH. Solutions of various buffer concentrations and pHs were prepared for each buffer system. One urease tablet (230 μM units/tablet) was placed in each solution at the beginning of the evaluation.

b. Preparation of acid/base blends

Three types of blends were prepared for evaluating the generation of CO_2 by the reaction of sodium carbonates with acids. These blends included a stoichiometric blend so that all the reactants are consumed in the reaction, a blend containing a 100% excess of carbonate, and a blend containing a 100% excess of acid. Blends were prepared by measuring appropriate amounts of the acid and carbonate into small vials. The vials were shaken until the powders were thoroughly mixed. Milli-Q water (10 mL) was added to each powder blend at the beginning of each evaluation.

c. Measurement of carbon dioxide generation

Measurement of carbon dioxide production was accomplished using the apparatus shown in Figure 2. Carbon dioxide was generated by putting a urease tablet in the reaction chamber along with 10 mL of a buffered substrate solution or by putting acid/carbonate powder blend into Milli-Q water. The chamber was then sealed quickly using a glass stopper. Prior to beginning each evaluation, the buret was filled to the highest mark with silicone oil. The increase in gas volume resulting from the evolution of CO_2 was determined by measuring the displacement in the height of the oil in the buret as a function of time.

3. Other systems

We also performed limited evaluations on two other pressure-generating systems which we thought might yield the desired release characteristics. These included foam production and water-absorbent polymers.

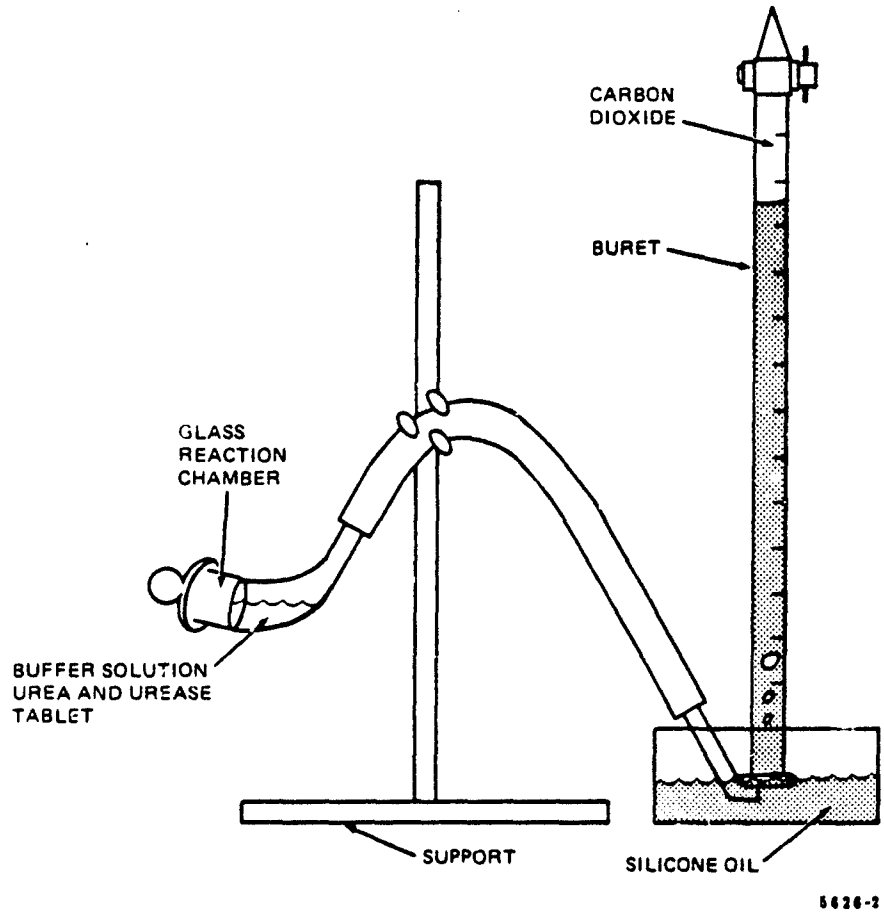

Figure 2. Apparatus for measuring the rate of carbon dioxide generation.

a. Foam production

Hypol 4000 (W. R. Grace and Company, Lexington, MA) is a viscous prepolymer which reacts vigorously with water to yield a semirigid polyurethane foam. Hypol is a commercially available compound. Our preliminary experiments indicated that Hypol expands 6 to 8 times its initial volume.

b. Water-absorbent polymers

In principle, it is also possible to exert a force on a container by expanding its contents. To apply this principle, we studied swelling of a commercially available absorbent polymer (Water-Lock J-400, Grain Processing Corporation, Muscatine, IA). This material is a polymer which absorbs about 100 times its own weight in water.

B. Fabrication and Evaluation of Demonstration Prototype

We constructed a prototype device from aluminum bar stock for the initial evaluation of the system. The prototype device contains three drug-loaded compartments: an initial bolus compartment and two reservoir compartments. The system was tested using a water-soluble dye as the model drug. The assembly plan for the prototype is given in Figure 3.

An aqueous dye solution was first placed in the initial bolus compartment. The piston was then spring-loaded and inserted into the body of the device. An aqueous dye solution of a second color was next placed in the bottom of the reservoir compartment. A neoprene spacer was placed around the lip of the drug-solution compartment, and a sandwich-type gasket containing an extensible membrane was placed on top of the spacer. A metal screen was then added. Finally, another neoprene spacer was placed, followed by a tall, hollow aluminum spacer. Water was introduced into the hollow aluminum spacer by either placing and rupturing a water-filled bladder after assembly or by immersing and capping the device under water.

The sandwich-type gasket mentioned above was fabricated to reflect the type of pressure-generating system being used. The sandwich was made from a thick neoprene gasket and various membranes. An extensible latex membrane was glued (usually cyanoacrylate or RTV silicone) to one surface of the gasket while a semipermeable membrane was glued to the other surface. For osmotic systems, a saturated salt solution was placed inside the sandwich. The sandwich was placed in the device in such a way that the latex membrane was exposed to the drug reservoir while the semipermeable membrane was exposed to the water. For gas-generating systems, a mixture of citric acid and sodium bicarbonate was placed in the sandwich. For water-absorbent polymers, filter paper (Whatman No. 1) was used instead of the cellulose acetate membrane. For the foam studies, no membrane was used.

After complete assembly, the experiment was initiated by removing the retainer pin for the piston leading to the bolus solution being rapidly injected. If a water bladder was present, it was ruptured by a side pin. In

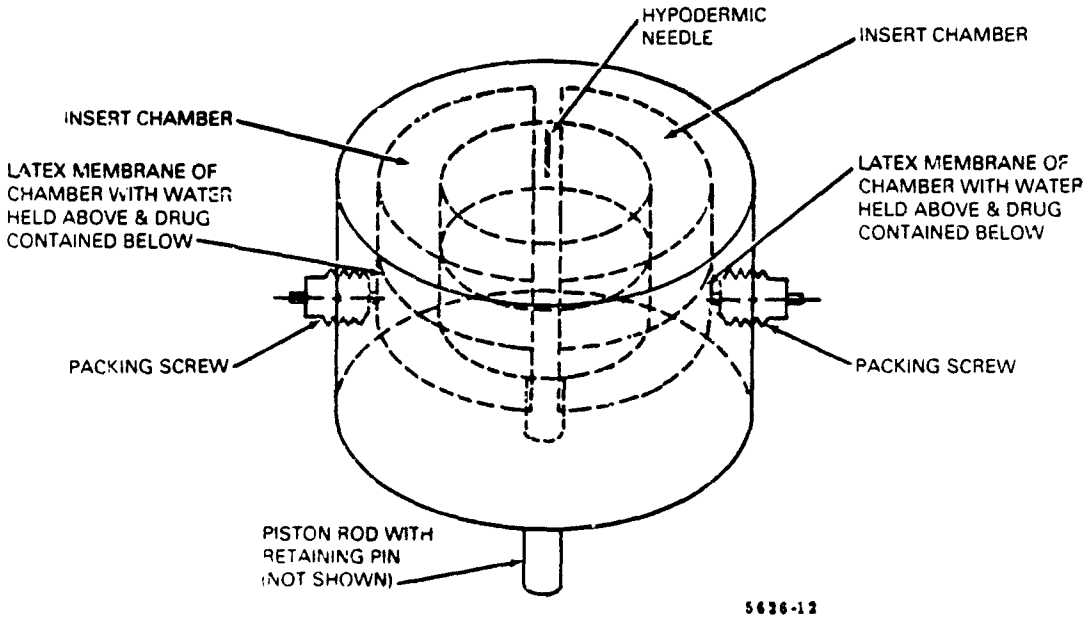

Figure 3. Prototype of generic drug-delivery device.

some experiments, the bolus injection was omitted to test only the long-term reservoir operation.

III. RESULTS AND DISCUSSION

A. Preliminary Evaluation

1. Osmotic system

We first examined the effect of prehydrating the membrane prior to testing. Immersion in water for 24 hr should allow the membranes to completely hydrate, thereby eliminating the time lag that would normally precede steady-state flux. Figure 4 illustrates the effect of prehydration on cellulose acetate membranes. Changes in lag time and flux are greater for the thick membranes because the water has a greater amount of membrane material to diffuse through. Because of the decreased lag time and increased flux afforded by prehydration, all membranes were immersed in water for 24 hr prior to testing.

Table 2 lists all the membranes prepared and tested at various salt concentrations. Figures 5 and 6 show the effect of membrane thickness on the flux of water across cellulosic membranes at transmembrane sodium chloride concentrations of 3 and 5 mol/L respectively. Polysulfone is not shown because no detectable osmotic flux occurred under these conditions. By varying cellulose acetate membrane thickness and salt-solution molarity, a range of volume changes spanning an order of magnitude can be achieved, as shown in Figure 7. The first-order character of the osmotic flux that is shown in all of the figures is a result of the declining salt concentration in the salt compartment. This can be avoided, if desired, by maintaining a saturated solution in the salt compartment throughout the period of delivery. This mechanism appears well suited as a regulatory driving force for the proposed drug-delivery system.

2. Gas-generating system

a. Enzyme/substrate system

At unit concentrations of enzyme and substrate, the reaction of urease and urea to produce carbon dioxide and ammonia is governed by two major factors. The first is that urease activity increases with pH from approximately pH 2 to pH 8. The second is the type and ionic strength of the buffer. Furthermore, carbon dioxide does not evolve as a gas, but remains in solution above approximately pH 5.5. By producing ammonia, the enzymatic reaction increases the pH of an initially acidic solution and shuts down carbon dioxide evolution when the pH reaches 5.5.

The volume and duration of evolution of carbon dioxide at pH 2.5 is proportional to the ionic strength of the phosphate buffer as seen in Figure 8. Figure 9 shows that these two factors are inversely proportional to pH.

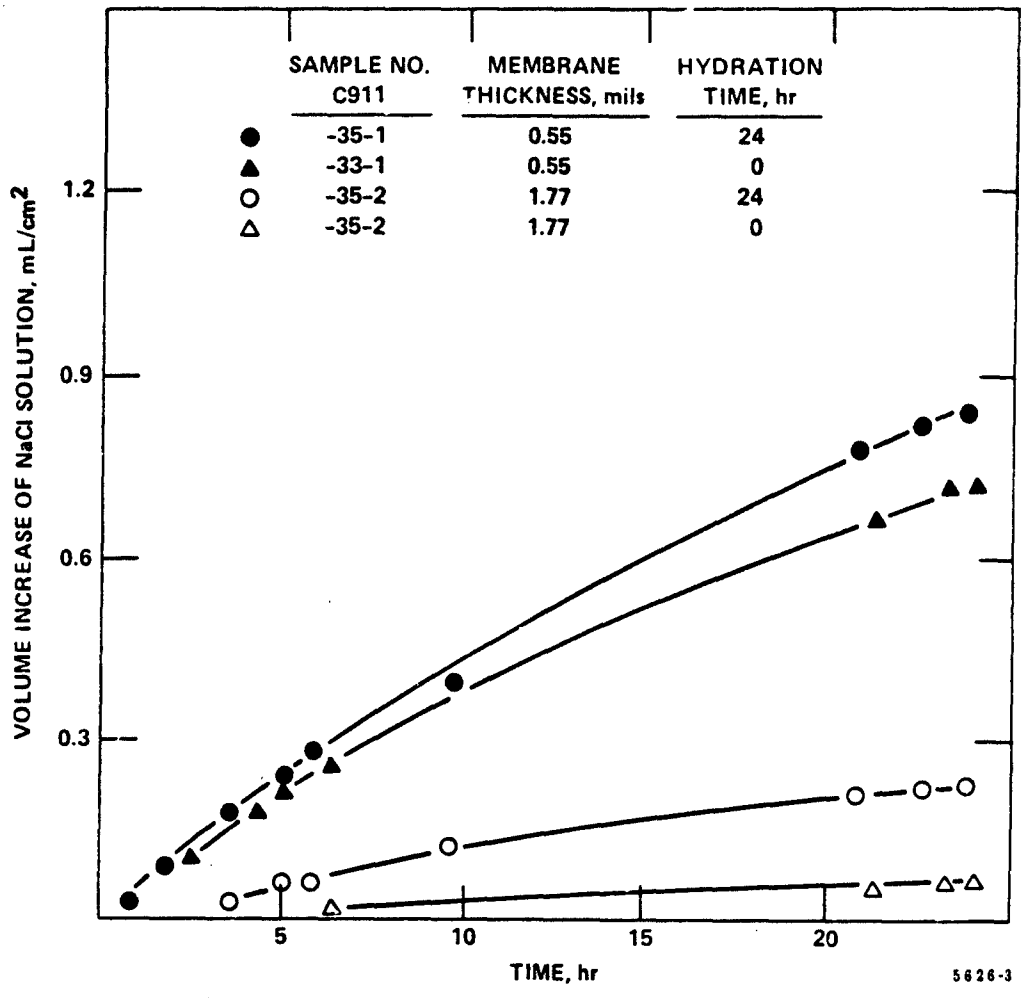

Figure 4. Prehydration effect on water flux across cellulose acetate membranes using a 3 M NaCl solution.

TABLE 2. LIST OF MEMBRANES EVALUATED

Sample No. C911-30	Membrane material	Thickness, mils	Molarity of NaCl solutions used to test samples
-1	Cellulose Acetate	0.55	1, 3, 5
-2	Cellulose Acetate	0.98	1, 3, 5
-3	Cellulose Acetate	1.77	1, 3, 5
-4	Ethyl Hydroxyethyl Cellulose	0.71	3, 5
-5	Ethyl Hydroxyethyl Cellulose	1.18	3, 5
-6	Cellulose Acetate Butyrate	1.10	3, 5
-7	Cellulose Acetate Butyrate	1.26	3, 5
-8	Udel Polysulfone	2.76	3, 5

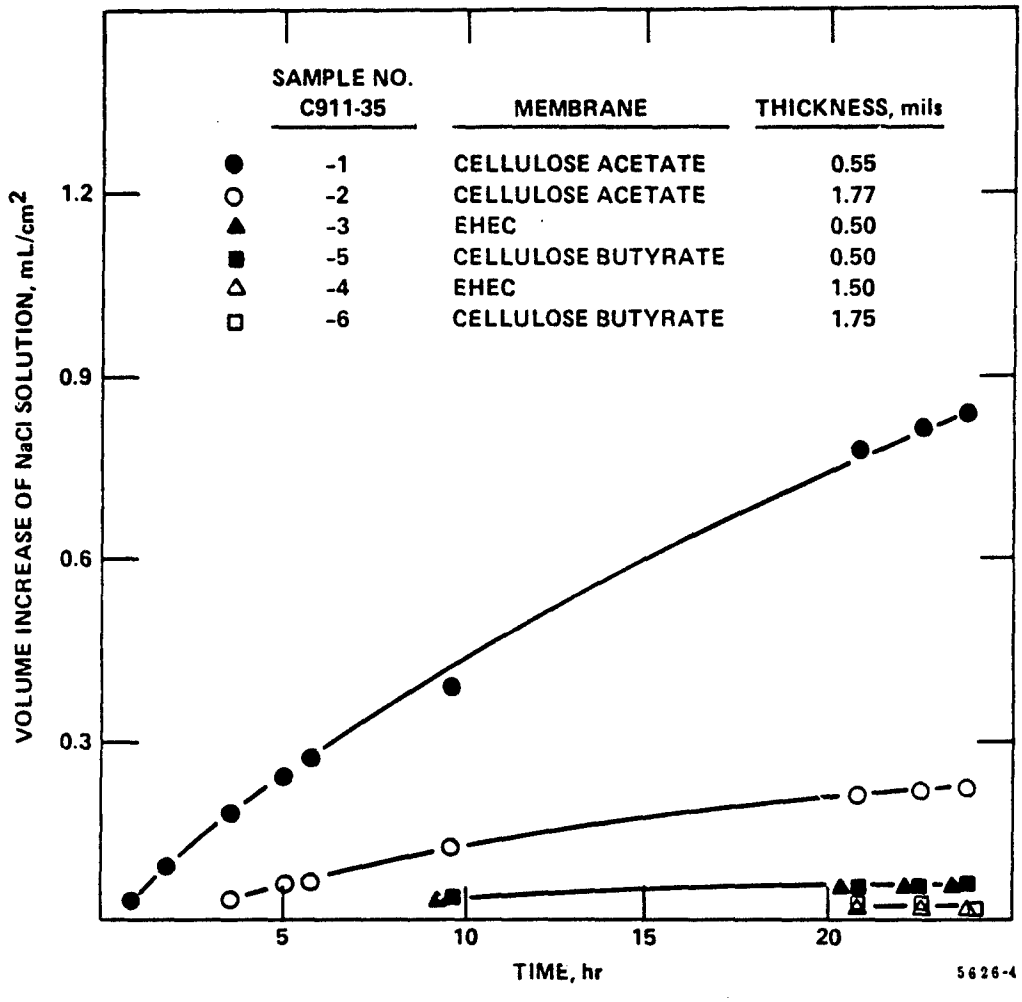

Figure 5. Water flux across various cellulose membranes using a 3 M NaCl solution.

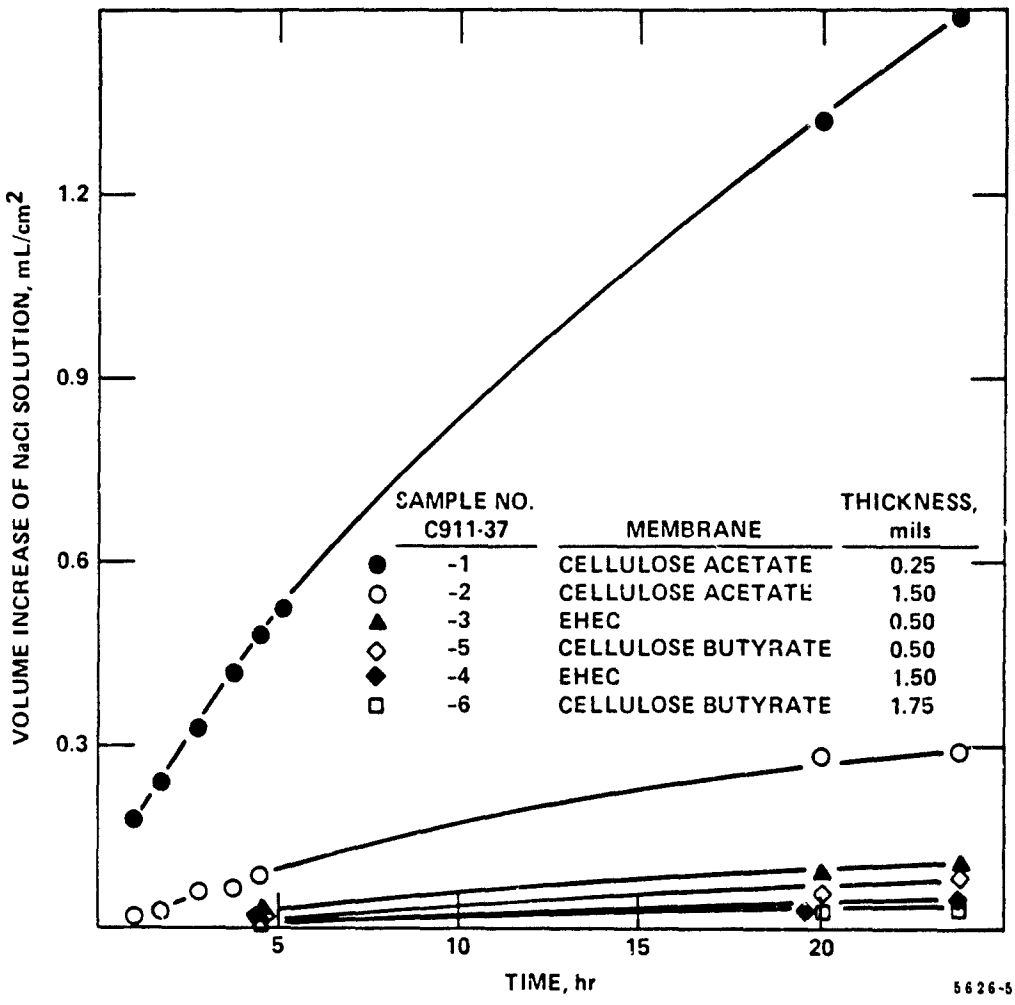

Figure 6. Water flux across various ceilulose membranes using a 5 M NaCl solution.

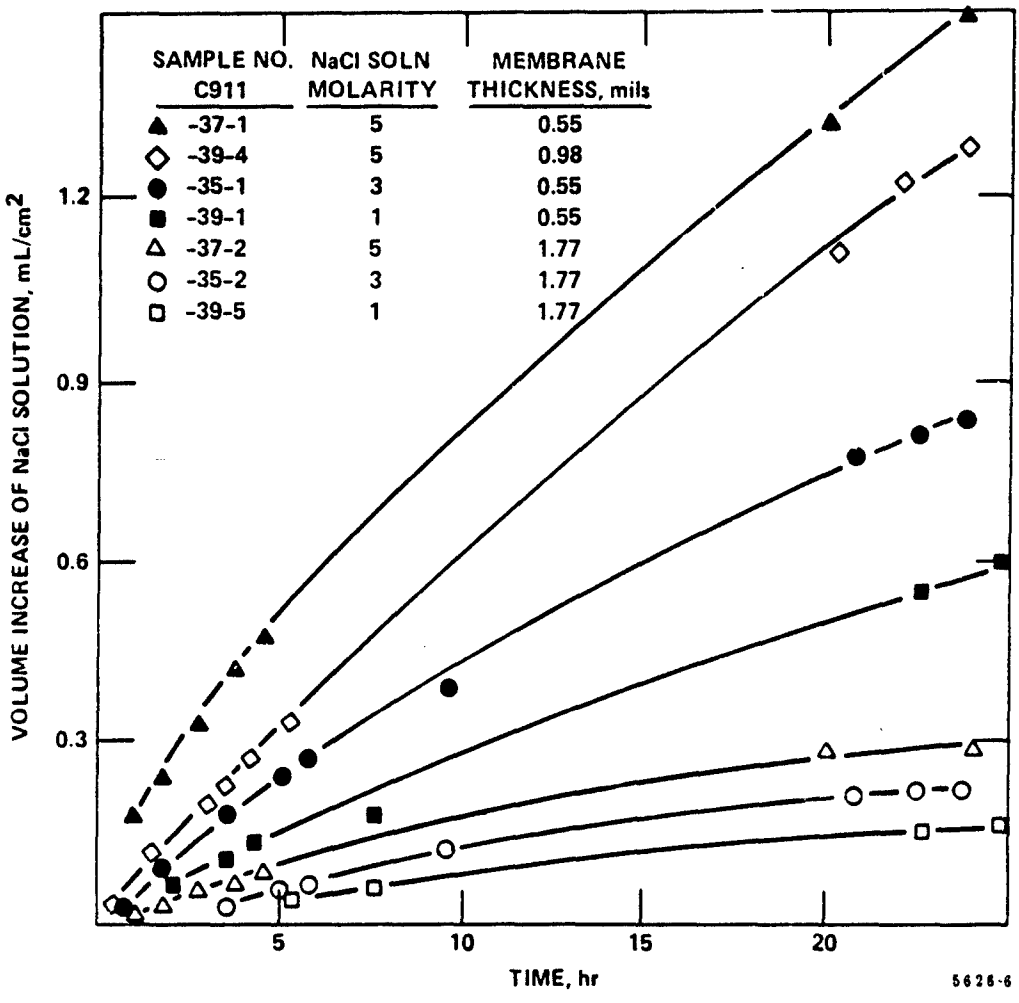

Figure 7. Effect of NaCl solution molarity and membrane thickness on water flux across cellulose acetate membranes.

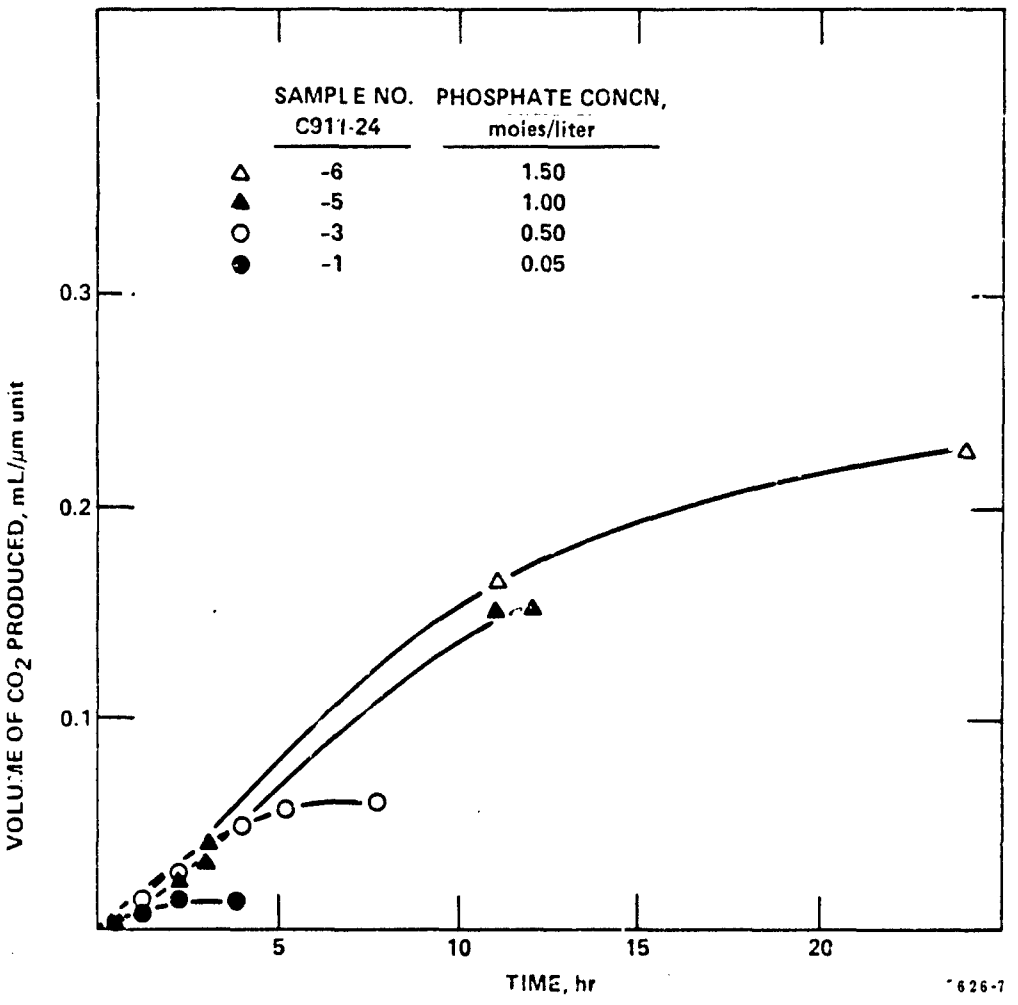

Figure 8. Effect of phosphate concentration on the evolution of CO_2, 2.4 M urea, pH 2.5.

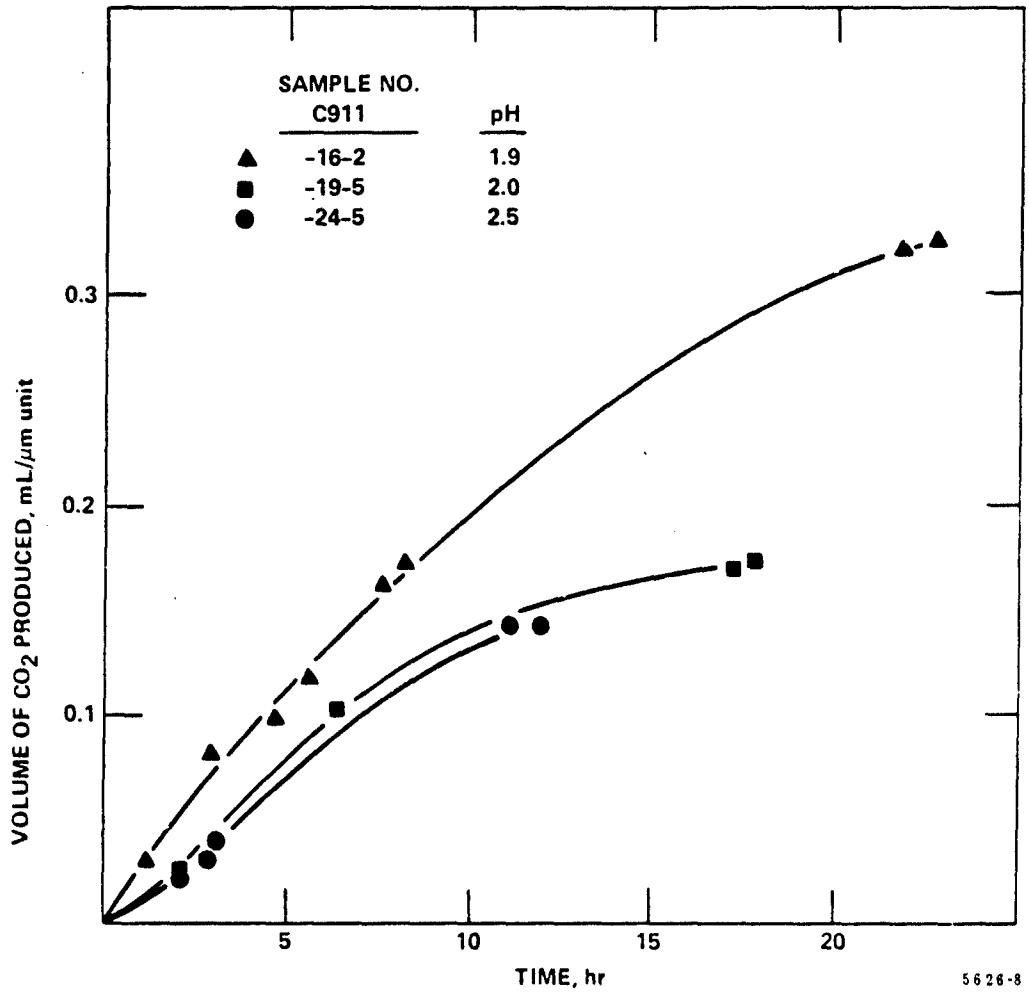

Figure 9. Effect of pH on the evolution of CO_2, 2.4 M urea, 1.0 M phosphate buffer.

However, the complexity of the system can create changes in these trends if the reaction initiates at another pH. This difference is noted by comparing Figures 8 and 10.

It is evident from the data that using sustained evolution of carbon dioxide for a driving mechanism is possible with the urea/urease system in a phosphoric acid/NaOH buffer. The other buffers containing DL-aspartic acid and formic acid were tested. Both appeared to inhibit the enzymatic reaction even under the correct pH conditions, and no production of carbon dioxide was detectable.

b. Acid/base system

The acids that were investigated were chosen on the basis of their dissociation constants to obtain a range of sustained generation rates. This did not occur in the candidate acid/sodium bicarbonate system. Reactions were rapid and short-lived as shown in Figure 11 for sebacic acid. The reaction involving stearic acid was extremely slow because of its insolubility and was not tested further. Reaction durations of approximately 24 hr were achieved with an acid/calcium carbonate system (Figure 12). The less-soluble carbonate seemed to be a greater rate-determining factor than the acid. The linearity of gas generation present in the osmotic and enzyme/substrate systems was not as prevalent in this system. However, this nonlinearity may be preferable for delivery of certain drugs.

B. Prototype Evaluations

1. Osmotic system

For this series of tests we chose components that would maximize the volume displacement. A saturated NaCl solution and a 0.55-mil cellulose acetate membrane were selected to provide a large driving force, good transfer rate, and relative ease of handling. The principal difficulty with this system is that of sealing the salt solution between the latex and cellulose acetate membranes via a neoprene gasket. The cyanoacrylate adhesive embrittled both the cellulose acetate and the neoprene, and the adhesive line failed as the membrane expanded. As an alternative to cyanoacrylate, we used RTV silicone to attach the membranes to the gasket. This bonded well to the latex but not to the cellulose acetate, and the salt compartment often leaked.

A secondary problem is that the displacement volume was too low and not in keeping with the values predicted in the preliminary studies. This is probably because of the opposing pressure presented by the latex membrane. This was obviated somewhat by the use of a much more distensible membrane made from condom latex. However, the delivery volumes were still unsatisfactory.

2. Acid/base system

Because of the rapid gas-generation capability of sodium bicarbonate and citric acid, we chose this system for our initial evaluations in situ. Approximately equal weights of each were placed between the membranes. After

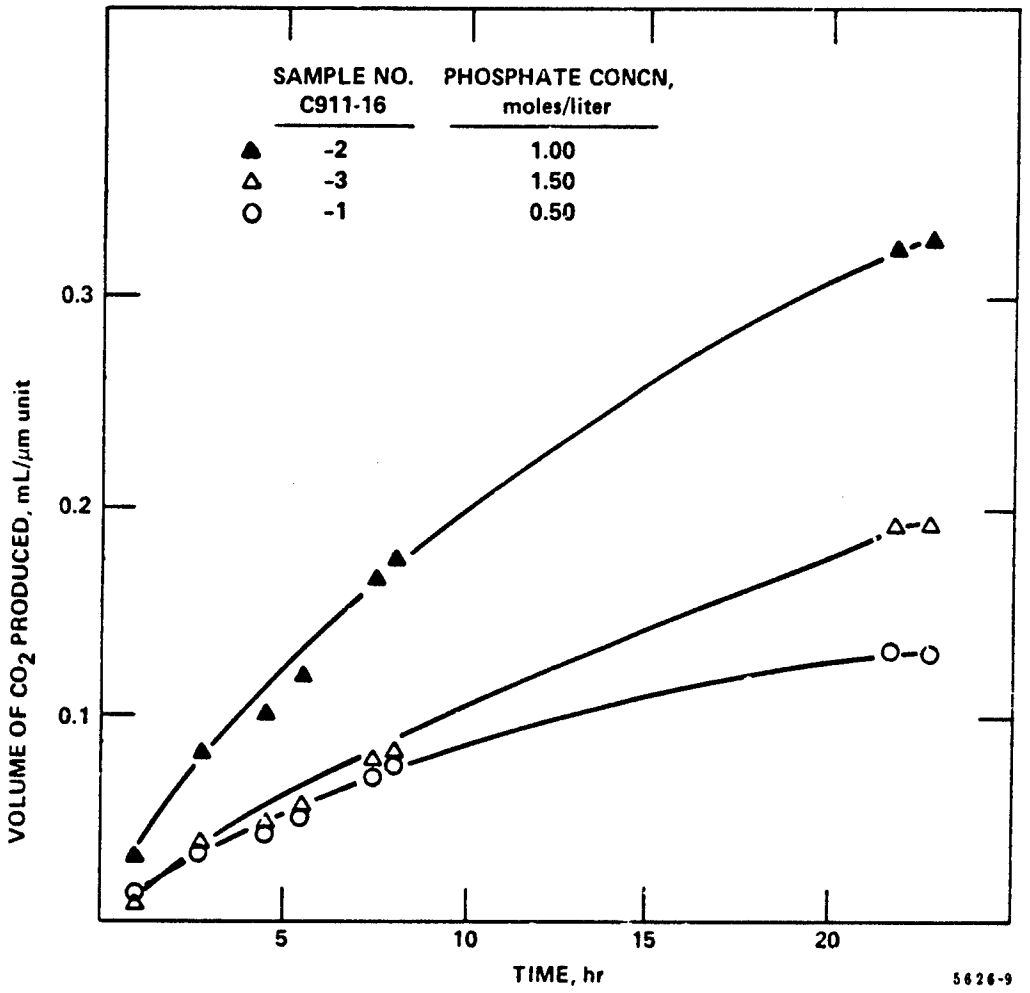

Figure 10. Effect of phosphate concentration cn the evolution of CO_2, 2.4 M urea, pH 1.9.

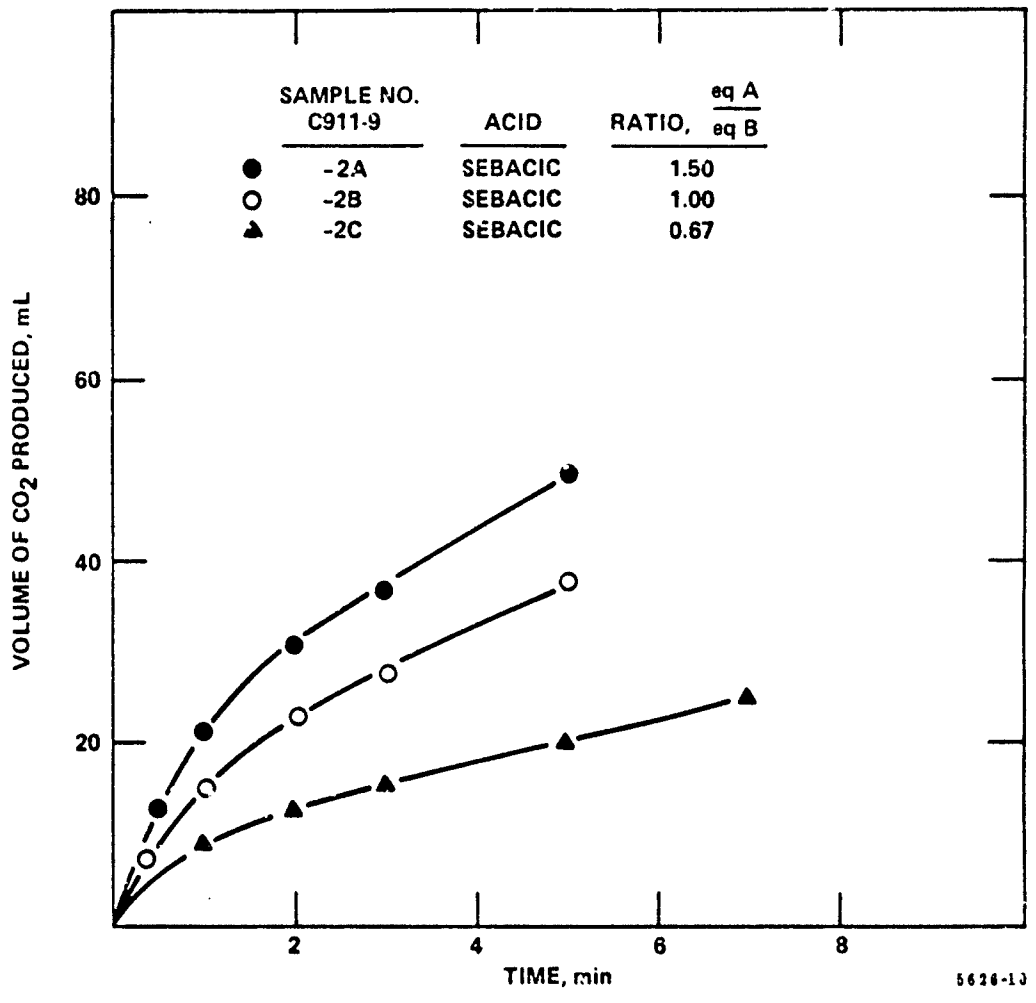

Figure 11. Carbon dioxide generation for acid/sodium bicarbonate system.

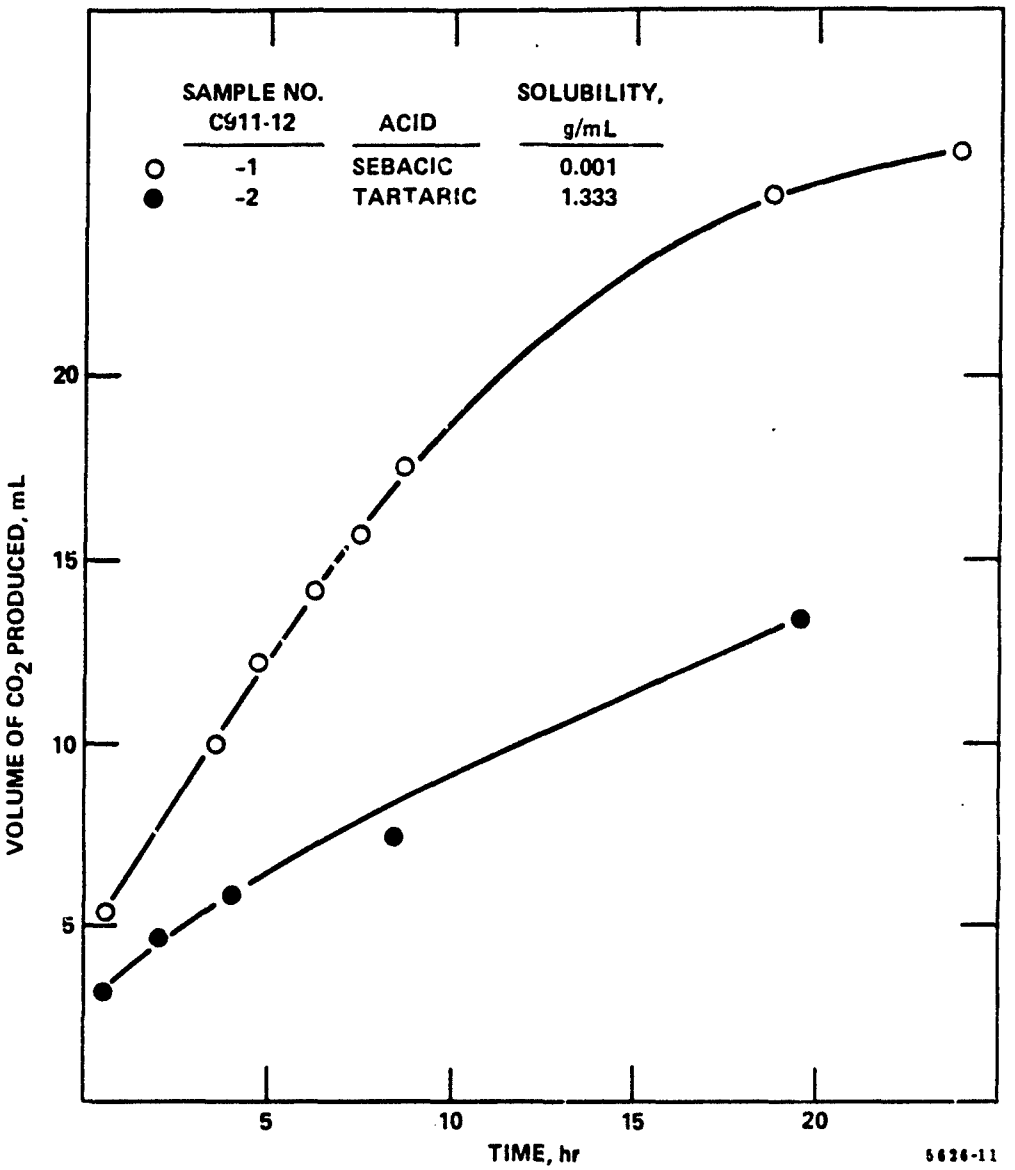

Figure 12. Evolution of CO_2 from organic acid/calcium carbonate mixtures.

about 18 hr, there had not been enough diffusion across the cellulose acetate to dissolve either compound. And we did not evaluate this delivery system further.

We then evaluated the acid/base generating systems without the use of a semipermeable membrane. The reagents were simply mixed together and placed on the surface of the latex diaphragm. The device was then assembled in the usual manner. The results of these experiments were dramatically different from those described above. The sodium carbonate/citric acid system began generating CO_2 as soon as the bladder was ruptured, and drug was delivered rapidly and steadily until the reservoir was exhausted. We next tried a reagent pair with a slower generating rate. A sodium carbonate and tannic acid system generated enough CO_2 to begin drug delivery 15 min after the bladder ruptured. The delivery rate was extremely slow and uniform. We completely immersed the device while this experiment was in progress so that we could determine if CO_2 was escaping. It was not. A calcium carbonate/acid reagent pair may well give even better results than those described above. Because of the extremely low solubility of calcium carbonate, very small quantities of this reagent can be used to maintain saturation and therefore constant generation rate. This means that relatively large quantities of CO_2 can be generated in a very small device.

3. Hydrophilic polyurethane Foam

The in situ evaluations of the foam were conducted without cellulose acetate membranes. The expansion volume of the foam is sufficient to cause membrane rupture. We placed a small amount of the prepolymer, Hypol 4000, on top of the latex. Upon sealing the assembled device, we noticed that delivery began almost immediately and continued at an approximately constant rate for 10 min. In none of these tests did we observe any leaking between the reservoirs. Figure 13 represents a typical release profile for this system. Obviously a delivery time of 10 min cannot be considered as sustained, controlled release. Therefore, while this delivery system is reliable and lends itself well to miniaturization, the high delivery rate renders it unsuitable in its current form. Two possible ways to improve this system are to incorporate an inhibitor to slow the polymerization or to insert a semipermeable membrane between the upper reservoir and the prepolymer. The membrane would have to be inserted in such a way as to prevent rupture or adhesive failure.

4. Water-swellable polymer

For this series of experiments, we placed a thin layer of Water-Lock over the latex and covered this with Whatman No. 1 filter paper. Delivery began approximately 5 min after assembly and continued for 8 hr. The release profile of dye using this system is shown in Figure 14. Of the 4 mL added to the drug reservoir, 2 mL was absorbed by the gel. This can be avoided by gluing the gaskets to the drug reservoir.

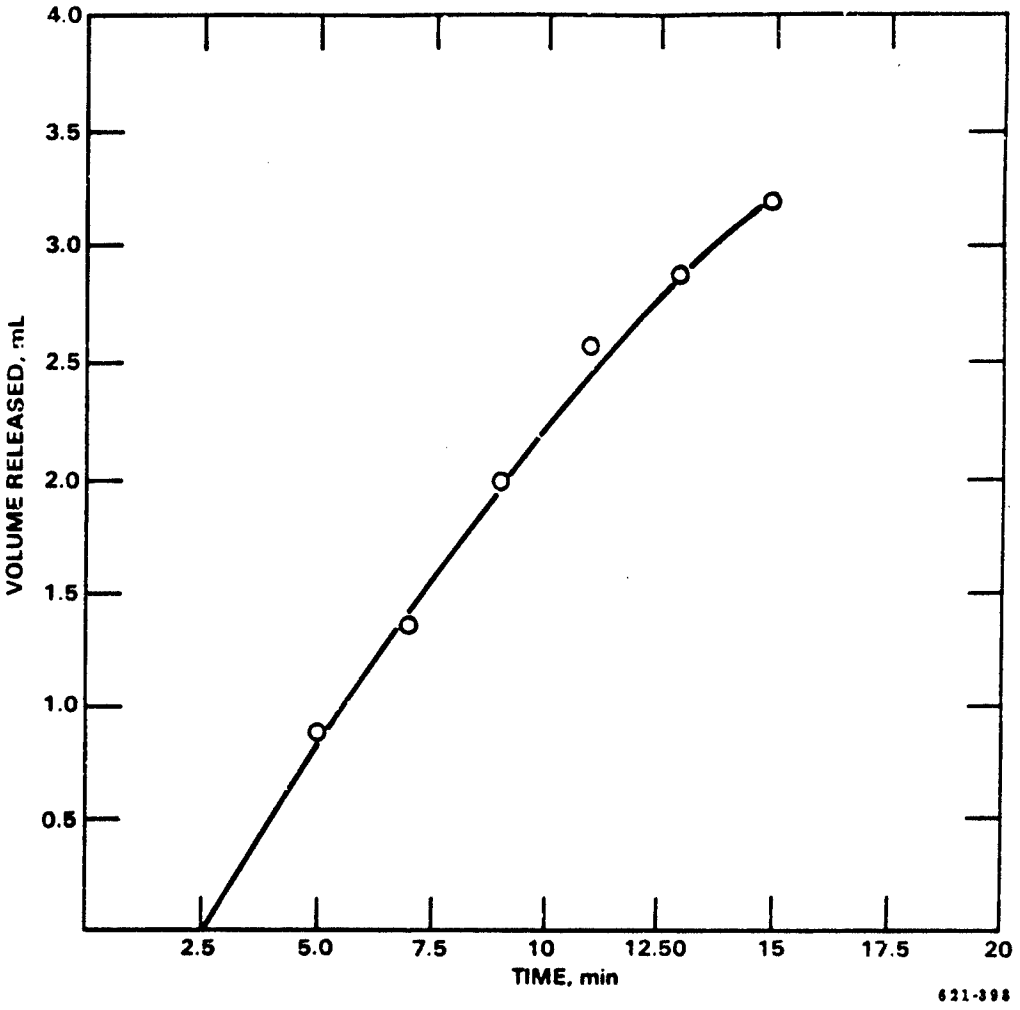

Figure 13. Volume of dye released vs.time for Hypol 4000.

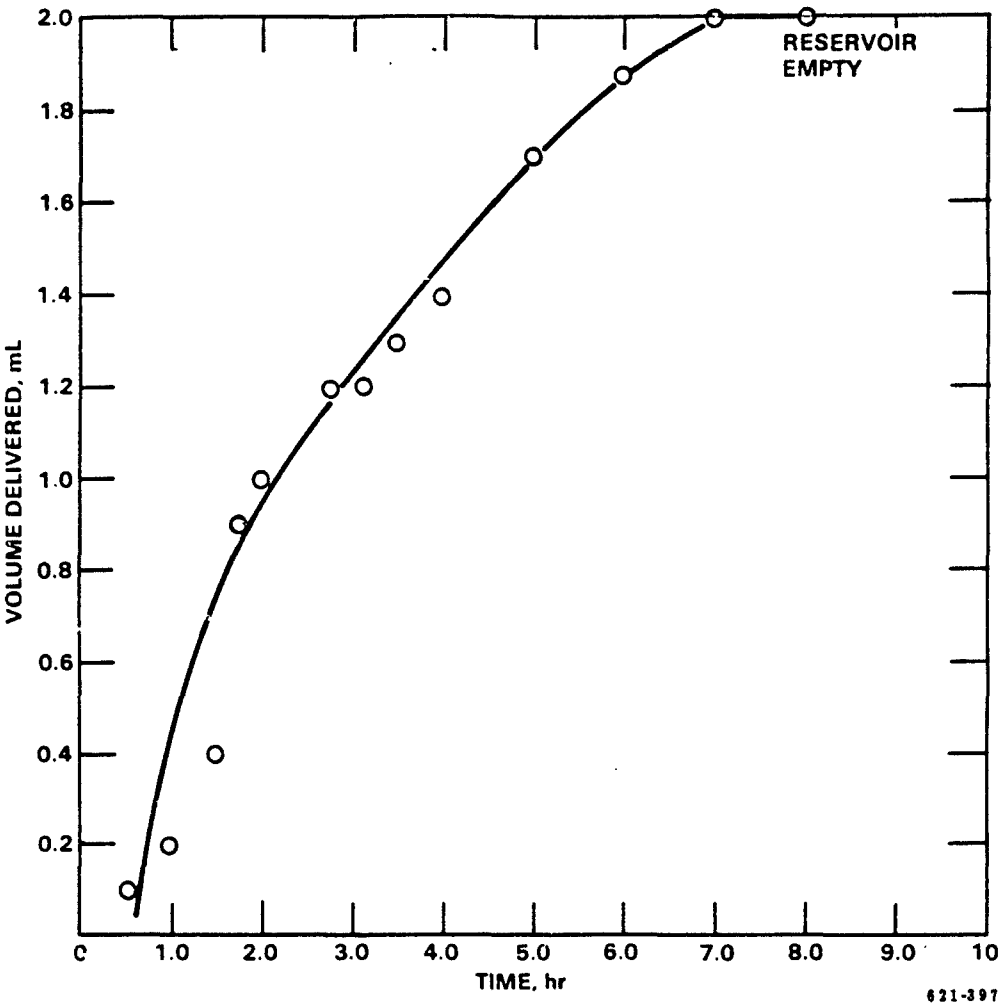

Figure 14. Volume of dye delivered vs. time for water-swellable polymer system.

IV. CONCLUSIONS AND RECOMMENDATION

Three driving-force mechanisms for a generic drug-delivery device were developed. All significant linearity in the preliminary tests showed and should be able to provide a sustained driving force for at least a 24-hr period. The osmotic system has a substantial range of delivery volumes and has parameters, such as membrane thickness and salinity, which can be manipulated easily for a specific application. The enzyme/substrate system demonstrates linearity of gas generation, a number of easily variable parameters such as pH and buffer concentration, and a distinct end point for gas evolution. Gas generation with the acid/base system is more first-order but still achieves a 24-hr duration. Swellable systems can also be used in the device but need considerable development.

The prototype device that we fabricated performed reasonably well in view of the difficulties that we experienced with the water- and gas-tight seals. We believe that sealing problems will be easily overcome by injection molding the device components and ultrasonically welding the seals and device housing.

In summary, we believe that the basic device design meets all of the criteria set forth by the Office of Naval Research. We feel that a gas-generating power source offers the best opportunity to minimize the overall size of the device. Our design should prove to be low in cost and useful for a wide variety of drugs. Accordingly, we recommend that the program be continued for a period of two years to finalize the design and conduct preliminary animal testing.

Approved by:

Richard L. Dunn

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Applied Sciences Department

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